



Trodelvy[®] (sacituzumab govitecan-hziy) Neutropenia and Growth Factor Support: Real-World Studies of SG in mBC

This document is in response to your request for information regarding Trodelvy[®] (sacituzumab govitecan-hziy [SG]), neutropenia, and use of growth factors in metastatic breast cancer (mBC) studies, including triple-negative breast cancer (TNBC) and hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer (BC). This response was developed according to principles of evidence-based medicine and contains data on SG monotherapy from real-world studies (N≥50).

Gilead continually assesses safety data from all sources for unidentified drug reactions and updates the product label information accordingly to reflect the safety profile of SG. Because case reports of potential adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. For this reason, Gilead does not provide information from post-marketing spontaneous reports.

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The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at:

www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Summary

Relevant Product Labeling¹

SG can cause severe, life-threatening, or fatal neutropenia as early as the first cycle of treatment. Neutropenia occurred in 64% of patients treated with SG. Grade 3-4 neutropenia occurred in 48% of patients. Febrile neutropenia occurred in 6% of patients. The median time to first onset of neutropenia (including febrile neutropenia) was 19 days (range: 1–1022 days). Neutropenia occurred earlier in patients with reduced UGT1A1 activity. Neutropenic colitis occurred in 1.4% of patients.

Primary prophylaxis with G-CSF is recommended starting in the first cycle of treatment in all patients at increased risk of febrile neutropenia, including older patients, patients with previous neutropenia, poor performance status, organ dysfunction, or multiple comorbidities.

Monitor ANC during treatment. Withhold SG for ANC <1500/mm³ on Day 1 of any cycle or <1000/mm³ on Day 8 of any cycle. Withhold SG for neutropenic fever. Dose modifications may be required due to neutropenia. Treat neutropenia with G-CSF and administer prophylaxis in subsequent cycles as clinically indicated or indicated in Table 2 of the SG FDA-approved prescribing information.

Incidence of Neutropenia and Use of Growth Factors: Real-World Data²⁻¹⁰

This summary presents neutropenia rates and growth factor use (as primary or secondary prophylaxis) during SG treatment in clinical practice, based on global real-world mBC studies.

Incidence of neutropenia and growth factor use on clinical outcomes, duration of SG treatment, and the occurrence of SG dose modifications is presented. In addition, the effect of the initial SG dose on neutropenia risk is examined.

Real-World Studies of SG Use in mBC

Incidence and Management of Neutropenia

Neutropenia prevalence and G-CSF use in mTNBC²

A US retrospective, observational cohort study assessed SG data from the Flatiron Health database to evaluate outcomes of patients with mTNBC who received SG in the 2L+ setting (N=381). The median (IQR) age of patients was 61 (52–69) y; 61% and 18% identified as White and as Black/African American, respectively. Patients received a median (IQR) of 2 (1–3) prior LoT in the metastatic setting. SG was administered to 31% of patients (n=118) in the 2L setting and 69% of patients (n=263) in the 3L+ setting.

Patients received a median (IQR) of 12 (5–21) SG doses over 6 (3–11) cycles. Of the patients with dosing data (n=308), 51% (n=157) had a dose reduction. Treatment duration is summarized in Table 1.

Table 1. SG DOT²

	All Patients (N=381)	SG in 2L (n=118)	SG in 3L+ (n=263)
Duration, median (IQR), mo	4 (1.9–7.6)	4.2 (1.6–8.1)	4 (2.1–7.4)

Safety

Incidence of Grade 2 and ≥3 neutropenia was 25% (n=94) and 27% (n=101), respectively. During SG treatment, 225 patients (59%) received G-CSF; 117 patients received G-CSF as prophylaxis (primary prophylaxis, n=77 [20%]; secondary prophylaxis, n=36 [9%]; both, n=4 [1%]). Grade ≥3 neutropenia occurred in 12 patients (10%) after any G-CSF prophylaxis and in 3 patients (4%) receiving primary prophylaxis. Median (IQR) time from the start of SG treatment to first onset of Grade ≥3 neutropenia was 48 (36–322) d; see Table 2 for results stratified by G-CSF use.

Table 2. Incidence and Time to First Onset of Grade ≥3 Neutropenia²

Grade ≥3 Neutropenia	G-CSF Use			
	Did Not Receive (n=156)	Primary Prophylaxis (n=77)	Secondary Prophylaxis (n=36)	Therapeutic G-CSF ^a (n=24)
n (%)	21 (13)	3 (4)	7 (19)	8 (33)
Time to onset, median (IQR), d	8 (8–22)	48 (36–322)	42 (36–56)	N/A

^aAdministered to treat neutropenia that occurred after the index date and before resolution of neutropenia or end of SG treatment.

Prevalence and risk factors of Grade 3 or 4 neutropenia and FN³

This single-center, retrospective study of patients with mTNBC or HR+/HER2- mBC (N=87) evaluated the safety profile of SG and sought to identify patient risk factors associated with SG-related Grade 3 and 4 neutropenia and FN. In the 77 patients who did not receive primary G-CSF prophylaxis, the median (IQR) age was 56.4 (47.3–65.4) y; 49% and 36% of patients identified as non-Hispanic White and non-Hispanic Black, respectively; 77% had mTNBC; 23% had HR+/HER2- mBC; and 68% had ECOG PS 0 or 1. Overall, the median (range) number of SG doses was 10 (1–90) over 5 (1–45) cycles.

Of the 77 patients who did not receive primary prophylaxis, 52 patients (68%) had neutropenia, and 38 patients (49%) had Grade 3 or 4 neutropenia; FN was reported in 3.9%. Secondary G-CSF prophylaxis was used in 35 patients with Grade 3 or 4 neutropenia, 14 patients with Grade 1 or 2 neutropenia, and 8 patients with an unknown grade of neutropenia; 3 patients with Grade 3 or 4 neutropenia did not receive G-CSF. All 10 patients who received primary G-CSF prophylaxis received pegfilgrastim. Secondary G-CSF prophylaxis included pegfilgrastim only (n=26; 50%), filgrastim only (n=15; 29%), and both filgrastim and pegfilgrastim (n=11; 21%). Dose reductions and interruptions related to Grade 3 or 4 neutropenia or FN are reported in Table 3.

Table 3. Dose Reductions and Interruptions Related to Grade 3 or 4 Neutropenia or FN³

Outcome, n (%)	SG (N=87)	No Primary G-CSF Prophylaxis (n=77)
Dose reduction due to Grade 3 or 4 neutropenia or FN	23 (26)	21 (27)
Dose interruption due to Grade 3 or 4 neutropenia or FN	33 (38)	32 (42)
Dose reduction or dose interruption due to Grade 3 or 4 neutropenia or FN	38 (44)	36 (47)
Prolonged neutropenia (>7 d)	9 (10)	9 (12)

Risk factors and Grade 3 or 4 neutropenia

Grade 3 or 4 neutropenia was reported at a higher rate in non-Hispanic Black patients than non-Hispanic White patients (61% vs 53%, respectively); however, the difference was statistically nonsignificant (aOR 1.58; 95% CI 0.51–4.9). The odds of Grade 3 or 4 neutropenia were lower in patients who identified as other races than non-Hispanic White (aOR 0.08; 95% CI 0.01–0.78). Other assessed factors that were not shown to be significantly associated with Grade 3 or 4 neutropenia included the following: age, receptor status, ECOG PS, baseline absolute neutrophil count, prior lines of myelosuppressive chemotherapy, bone metastasis, surgery within 3 months, liver and renal function, and SG starting dose.

Neutropenia prevalence and G-CSF use in mBC⁴

A single-center, retrospective cohort mBC study examined electronic health records for clinical features, prior treatments, safety outcomes, and use of G-CSF in patients who had received SG (N=74). The median (range) age of patients was 56.5 (28.4–81.1) y. Patients with mTNBC had received a median (range) of 2 (0–5) previous chemotherapy regimens. Patients with HR+/HER2- mBC had received a median (range) of 8 (2–14) prior LoT, including 4 (0–8) lines of chemotherapy. The median (range) duration of SG therapy was 4.4 (0.26–39.8) mo for mTNBC patients and 1.9 (0.26–15.6) mo for those with HR+/HER2- mBC.

Rates of any-grade and Grade 3 neutropenia are shown in Table 4. A total of 8 patients (10.8%) were hospitalized for SG-related neutropenia with a median (range) stay of 3.5 (1–10) d. About half of all dose delays were due to neutropenia.

Table 4. Incidence of Neutropenia⁴

Outcomes, n (%)	All Patients (N=74 ^a)	mTNBC (n=45)	HR+/HER2- mBC (n=27)
Any-grade neutropenia	60 (81.1)	37 (82.2)	21 (77.8)
Grade 3 neutropenia	39 (52.7)	25 (55.6)	12 (44.4)
Neutropenic fever	5 (6.8)	4 (8.9)	NR
Dose delays	-	18 (40)	8 (29.6)
Due to neutropenia	-	7 (15.6)	4 (14.8)
Dose reductions	-	21 (46.7)	18 (66.7)
Due to neutropenia	-	7 (15.6)	4 (14.8)

Abbreviation: NR=not reported.

^aTwo patients (2.7%) with mixed receptor expression were classified as HR+/HER2+ mBC.

Most patients (86.5%; n=64) received G-CSF during SG treatment (Table 5). Rates of primary and secondary prophylaxis varied for patients with mTNBC and HR+/HER2- mBC.

Table 5. Incidence of G-CSF Use⁴

n (%) or %	Filgrastim	PEG-Filgrastim	Primary Prophylaxis	Secondary Prophylaxis
G-CSF use	62 (83.8)	7 (9.5)	34 (45.9)	24 (32.4)
mTNBC	-	-	37.8	40
HR+/HER2- mBC	-	-	55.6	22.2

Neutropenia Prevalence, G-CSF Use and Impact on DOT

Two US studies have evaluated SG data from the IntegraConnect PrecisionQ database, specifically examining the use of G-CSF and its effect on DOT.^{5,6}

Neutropenia prevalence, G-CSF use and impact on DOT in patients with cancer⁵

Data were assessed for neutropenia prevalence, G-CSF use and impact on DOT in 447 patients (cancer type was not reported). Patients were on average (median) 58.5 (60) y; 69% and 15% identified as White/Caucasian and as Black or African American, respectively. A total of 98% of SG-treated patients developed neutropenia; of these, 61% received G-CSF.

Median DOT was 119.5 d for patients with ≥12 mo follow-up (n=330); see Table 6 for the median DOT in patients who did and did not receive G-CSF.

Table 6. DOT and G-CSF Use⁵

G-CSF Use	Patients (n)	DOT, Median (Range), d	P-Value
Received	204	147 (7–942)	<0.001
Did not receive	126	97 (1–1013)	

G-CSF use and impact on SG DOT in mTNBC⁶

Data was stratified by G-CSF use and assessed for DOT with SG in patients with mTNBC (N=337). The median (IQR) age at first treatment was 58.3 (49–67) y; 65%, 17%, and 2% identified as White, Black/African American, and Asian, respectively. The median (IQR) time

from initial BC diagnosis to the first SG use was 3.3 (1–6) y. Of the patients with ECOG data, 28%, 49%, 11%, 1%, and 1% were ECOG PS 0, 1, 2, 3, and 4, respectively.

A total of 202 patients (60%) used G-CSF. For primary prophylaxis (46% of cases), 65% used long-acting, 34% short-acting, and 1% both agents. For secondary prophylaxis or treatment (54% of cases), 65% used short-acting, 35% long-acting, and 1% both. DOT was stratified by G-CSF use (Table 7).

Table 7. SG DOT Stratified by G-CSF Use⁶

G-CSF Use	Received	Did Not Receive	Primary Prophylaxis	Secondary Prophylaxis or Treatment	Long-Acting	Short-Acting
DOT, median (IQR), d	137 (71–239)	85 (44–188)	134 (65–241)	139 (71–239)	155 (72–246)	134 (71–224)

Initial SG Dose and Risk of Neutropenia⁷

A US retrospective, single-center cohort study evaluated the relationship of neutropenia and different starting doses of SG (10 mg/kg [70%], 7.5 mg/kg [22%] or 5 mg/kg [8%]) in 366 patients with HER2- mBC. Patient demographics and disease characteristics, treatment patterns, safety outcomes, and G-CSF use were evaluated. To control for confounding variables, inverse probability weighting based on propensity scores was applied.

Results showed that dose reductions were more common when patients initiated SG 10 mg/kg (42%) vs 7.5 mg/kg (16%); 66% of reductions were due to neutropenia. Three patients discontinued treatment due to toxicity. After adjusting for age, prior LoT, and prophylactic G-CSF use, patients who initiated SG with 10 mg/kg had a 2.8-fold higher OR of Grade 3 or 4 neutropenia vs those initiating SG with 5 mg/kg (OR 2.77; 95% CI 1.29–6.27; $P=0.011$); DOT was shorter with the 5 mg/kg dose. Age was not associated with neutropenia risk after adjusting for starting dose, prophylactic G-CSF use, and prior LoT.

There was significantly less Grade 3-4 neutropenia with prophylactic G-CSF use (OR 0.12; 95% CI 0.07–0.18; $P<0.001$) when controlling for age, prior LoT, and starting dose. Prophylactic G-CSF was most frequently used in patients who started treatment at reduced doses, but utilization rates did not differ by age.

Impact on Efficacy Outcomes With Prophylactic G-CSF

Impact of G-CSF prophylaxis on OS and TTD⁸

The IntegraConnect PrecisionQ database in the US was used to evaluate the impact of prophylactic G-CSF use (defined as use within 8 d of SG initiation) on TTD and OS among patients with mTNBC who had received SG (N=615). Patients with a documented neutrophil count <1500/mcL were excluded. Most patients were White (67%), 41% had an ECOG PS 1, and 88% did not receive prophylactic G-CSF. Median (IQR) age at SG initiation was 60 (53–69) y. Age, race, and ECOG PS did not significantly differ by prophylactic G-CSF use.

At 4 mo, the cumulative incidence of neutropenia was significantly higher among those who did not receive prophylactic G-CSF (42% vs 30%; Gray's test $P=0.002$). Median TTD and OS did not significantly differ by prophylactic G-CSF use. From 0 to 4 mo, patients who did not receive prophylactic G-CSF were >2 times more likely to die than those who received prophylactic G-CSF <8 d of SG initiation (HR 2.37; 95% CI 1.22–4.59; $P=0.011$). After 4 mo, the impact of not receiving prophylactic G-CSF on OS was lower (HR 1.02; 95% CI 0.79–1.5; $P=0.4$). There

was no significant difference in TTD between patients who did and did not receive G-CSF in either time interval.

Impact of primary G-CSF prophylaxis on PFS and OS⁹

The impact of G-CSF as primary prophylaxis on real-world clinical outcomes and treatment-related AEs was evaluated in a multinational cohort of patients with mTNBC who had received SG (N=303). Baseline characteristics were balanced for prior systemic treatment for early-stage disease, the number of prior LoT in the metastatic setting, comorbidities, metastatic sites, and prior episodes of FN. However, there were more patients with an ECOG PS of 0 among patients who received primary prophylaxis than in patients who did not receive primary prophylaxis (50% vs 37.1%; $P=0.034$).

Primary prophylactic G-CSF use was not associated with improved PFS or OS (Table 8).

Table 8. Impact of Primary G-CSF Prophylaxis on PFS and OS⁹

G-CSF Primary Prophylaxis	Median PFS, mo		PFS at 6 mo, %	Median OS, mo		OS at 12 mo, %
	%	P-Value		%	P-Value	
Received	4.2	0.2	38.5	10.9	0.95	44.9
Did not receive	5.1		42.1	11.6		47.1

There were no statistically significant differences in the rates of all-grade AEs between groups. There was a lower incidence of Grade ≥ 3 neutropenia in patients who received G-CSF primary prophylaxis than in patients who did not receive primary prophylaxis (33% vs 50.7%, respectively; $P=0.005$), but there was not an associated reduction in FN rates (4% vs 4.4%; $P=1$). Of the patients who did not receive primary prophylaxis, 74.4% eventually required secondary G-CSF support. Only 17.2% of patients received SG without any G-CSF support.

Impact of Primary G-CSF Prophylaxis on Neutropenia¹⁰

A UK retrospective, observational, case-controlled study that included data from 13 National Health Service Trusts evaluated the impact of G-CSF as primary prophylaxis on the incidence of neutropenic sepsis, Grade 3 or 4 neutropenia, and dose delays and reductions in patients with mTNBC who received SG (N=217).

The addition of primary G-CSF prophylaxis reduced both the proportion of patients who had ≥ 1 episode of FN and the proportion of patients who had ≥ 1 episode of Grade 3 or 4 neutropenia Table 9. Reduction in FN and Grade 3 or 4 neutropenia was also observed when per cycle or dose was analyzed. More dose delays were observed in patients who received primary G-CSF prophylaxis; however, the reason for the delay was not documented in all cases.

Table 9. Impact of Primary G-CSF Prophylaxis on Neutropenia¹⁰

Outcomes	Primary G-CSF Prophylaxis (n=87)	No Primary G-CSF Prophylaxis (n=130)
Number of cycles	519.5	976
Previous LoT, mean (median [range])	2.3 (2 [0–6])	2.4 (2 [1–7])
Number of cycles of SG, mean (median [range])	6 (4.5 [0.5–24])	7.6 (6.5 [0.5–30])
Number of doses of SG, mean (median [range])	11.9 (9 [1–42])	13.8 (12 [1–41])
Dose intensity, mean (median [range]), %	83 (83 [43–100])	85 (84 [43–100])

Outcomes		Primary G-CSF Prophylaxis (n=87)	No Primary G-CSF Prophylaxis (n=130)
Neutropenia	Overall episodes, n	87	263
	Rate per dose, %	8.6	15.5
	Patients with ≥1 episode of Grade 3-4, n (%)	13 (14.9)	38 (29.2)
	Grade 3-4 episodes, n	16	68
	Rate Grade 3-4 per dose, %	1.6	4
FN	Patients with ≥1 episode, n (%)	6 (6.9)	25 (19.2)
	Episodes, n	11	29
	Rate per cycle, %	2.1	3
Dose delays	Episodes, n	114	108
	Rate per cycle, %	21.9	11.1

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Abbreviations

2L=second-line
2L+=second-line and later
3L=third-line
AE=adverse event
ANC=absolute neutrophil count
aOR=adjusted odds ratio
BC=breast cancer
DOT=duration of therapy
ECOG PS=Eastern Cooperative Oncology Group Performance Status

FN=febrile neutropenia
G-CSF=granulocyte colony-stimulating factor
HR+/HER2-=hormone receptor-positive/human epidermal growth factor receptor 2-negative
LoT=lines of treatment
mBC=metastatic breast cancer
mTNBC=metastatic triple-negative breast cancer

OR=odds ratio
OS=overall survival
SG=sacituzumab govitecan-hziy
TNBC=triple-negative breast cancer
TTD=time to treatment discontinuation

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at:

www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

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